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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TURNER, SHARON L	
ART UNIT	PAPER NUMBER
1647	20

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/181,311	LEE ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-9 and 31-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9 and 31-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Amendment

1. The amendment filed 1-8-03 has been entered into the record and has been fully considered.

2. Claims 7-9 and 31-39 are pending.

Rejections Maintained

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 7-9 and 31-39 stand rejected under 35 U.S.C. 101 as set forth in Paper No's: 11 (8-16-00), 15(5-9-01) and 22 (7-3-02) because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 7-9 and 31-39 also stand rejected under 35 U.S.C. 112, first paragraph as set forth in Paper No's: 11 (8-16-00), 15(5-9-01) and 22 (7-3-02). Specifically, since the claimed invention is not supported by either a specific and substantial, asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants note their previous arguments that genes identified as being up- or down regulated during differentiation or migration of smooth muscle cells are specifically useful as diagnostic markers of numerous diseases as specified at pp. 1-2 and p. 45, lines 9-23. Applicants argue that the utility guidelines state that "an assay method for identifying compounds that themselves have a 'substantial utility' define a 'real world' context of use." Applicants conclude that since the claimed assay methods identify genes which themselves have a substantial utility, the assay methods define a real world context of use. In particular applicants argue that genes that are up or down

regulated during differentiation of neural crest cells into smooth muscle cells can be used as markers of the stage of differentiation of these cells and thus as diagnostic markers for predicting whether a subject has an increased probability of developing an occlusive arteriosclerotic disease. Applicants argue that the presence of differentiated or undifferentiated cells alone would be indicative of the disease or lack thereof. Applicant's invention is identified as teaching the artisan to screen for genes that are correlated with a particular differentiation state of the cell and thus the likelihood of developing arteriosclerosis. Applicants point to the disclosure of ACLP expression that is up-regulated in differentiated smooth muscle and that the absence of ACLP in vascular smooth muscle would be indicative of cellular de-differentiation and a predisposition to artiosclerotic disease. Additionally applicants point to Watanabe et al., 91(5):382-9, 2002 as disclosing a gene discovered using the claimed methods that correlates with the differentiation into smooth muscle. In particular Applicants argue that determining the level of mrf2 allows the artisan to ascertain the differentiation state and the likelihood of developing arteriosclerotic disease.

Applicant's arguments filed 1-8-03 have been fully considered but are not persuasive. Applicant's argument presupposes that the genes identified as being up or down regulated are immediately useful as prognostic or diagnostic indicators of arteriosclerotic disease. However, the correlation of such gene expression as a diagnostic or prognostic of arteriosclerotic disease has yet to be shown and is not discerned via the claimed method. Neither ACLP or mrf2 are shown to be correlated to, diagnostic or prognostic of artiosclerotic disease and thus a discovery of use therefore is not complete until such data is shown. The instant assay fails to correlate any particular gene product with any particular disease, but merely contemplates that such may be discovered by screening for players which are up- or down-regulated in a differentiating model system. The method does not teach how the artisan should use

either result. While an occlusive arteriosclerotic disease is contemplated by the specification as being a disease which would be likely to be associated with genes which were up- or down-regulated as claimed, no correlation between any such particular gene product and occlusive arteriosclerotic disease in patients has been disclosed. The "substantial utility" definition in examples A-E make clear those utilities which cannot be considered as substantial, including utilities wherein basic research is involved, methods of treating unspecified diseases or conditions, methods of assaying for or identifying a material that itself has no "specific and/or substantial utility", a method of making a material with no specific, substantial and credible utility and claims to intermediate products for use in making a final product with no specific, substantial and credible utility. In the instant case it appears that perfection of the required correlation would require further research to identify those genes that correlate with a particular disease state. Alternatively one could confirm a gene's utility in either assays, screens or other methods which provide a specific, substantial and credible use. As previously set forth, because the claimed invention does not provide a diagnostic correlation of disease incidence, likelihood or even of the cellular differentiation state, applicants claims are directed to generally recognized research methods for which alone there is no specific and substantial utility or well established utility. Identification of genes which are up or down regulated under various conditions, while a common research practice does not in and of itself provide immediate benefit absent a teaching of the significance and benefit provided by the use of the method and the indication or outcome that the method achieves. Merely identifying a gene that is up or down regulated places no particular significance, meaning or use on the research data. There is no guidance in the claim as to how the up or down regulated genes should be used to indicate any such disease or state. Without such the method at most appears to be a

general research plan at the end of which the artisan is only provided various data points but for which no direct benefit or use is provided.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

6. Claims 36-38 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 recites the term "smooth muscle cell differentiation medium" whereas claims 36-38 and 39 recite "smooth cell differentiation medium." The term as used in claims 36-38 and 39 lack clear antecedent basis in the claim. The claims should be amended to be consistent with the terminology of claim 31.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

8. Claims 7, 31, 32, 34-35, and 37-39 stand rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al., US Patent 5,672,499 filed June 7, 1995, issued September 30, 1997 and Claims 7, 32, 34 and 35 are rejected under 35 U.S.C. 102(e)

as being anticipated by Anderson et al., US Patent 6,001,654 filed April 25, 1997, issued Dec. 14, 1999.

Claim 31 is anticipated via Anderson et al., '654 and '499 as both references teach differentiation to smooth muscle cells in culture media comprising for example standard media with fetal bovine sera at 1 mg/ml.

Claim 37 is anticipated via Anderson et al., '499 and claim 38 is anticipated via Anderson et al., '654 as the '499 patent teaches smooth muscle cell differentiation in standard media with fetal bovine sera with no exogenously added TGF-beta, whereas the '654 patent teaches smooth muscle differentiation in media with TGF-beta added. Thus, the reference teachings anticipate the claimed invention, see in particular Example 11 of the '654 patent.

Claim 39 is anticipated via the '654 and '499 patents as culture of the neural stem cells is provided for example in MEM or L15 media containing for example essential and nonessential amino acids and NaCl, see in particular Example 2.

As applicants continue to address the references jointly the rejection is also addressed jointly as the references are cumulative.

Applicants argue that the references teaching are prophetic. Applicants apparently argue that the Examiner's 103 rejection acknowledges that the method of claim 7 was not performed with immortalized cells. Applicants further argue that the references fail to teach differentiation of immortalized neural crest cells into smooth muscle cells, that the reference is only prophetic. Applicants further submit that primary culture cells are not immortalized as recognized in the art. Applicants do not apparently acknowledge a prophetic example of immortalizing neural crest stem cells. Applicants

submit that their population of smooth muscle cells are nearly 100% smooth muscle cells as noted at p. 15, line 4 but that neither patent teaches every (these) elements of the claims. Applicants argue that the references do no teach a method for identifying a gene that is up- or down-regulated during the differentiation of neural crest cells into smooth muscle cells. Applicants argue that the references merely use known smooth muscle cell marker to establish their presence in culture.

Applicants arguments filed 1-8-03 have been fully considered but are not persuasive. As recognized in the art, the '654 and '499 references teach examples of immortalized neural crest stem cells which are immortalized in particular as disclosed at column 19, lines 27-55 of the '654 patent, including via transforming oncogenes of the preferred embodiment, oncogene v-myc, see also column 31, including immortalization of NCSC's with retrovirus harboring an oncogene selected from the oncogenes identified herein, such as v-myc. The procedures for such transformation and immortalization of neural crest stem cells is disclosed in particular at columns 31, line 45-column 32, line 25 of the '654 patent. Thus, the Anderson reference discloses immortalization of neural crest stem cells via v-myc transformation as claimed. The methods are provided, are commonly known in the art and thus are deemed enabling. Thus, the claimed invention is anticipated by the prior art disclosure. As previously set forth it is noted that the method of Anderson results in the differentiation of smooth muscle cells and the identification of the genes alpha smooth muscle alpha-actin, peripherin and calponin which are up regulated upon differentiation in culture to smooth muscle cells, see for example Figure 20, 22, claims 6 and 21. Such up and down regulation does identify gene expression in the culture that is exactly what applicants method apparently is intended to do. The '654 and '499 references acknowledge multiple ways of performing such analysis as widely recognized in the art. For example as applicants point out, column 33 of the '654 patent, lines 26-31, lines 58-67 and

column 34, lines 1-6 disclose such measurement via the use of antibodies. Thus, the method identifies genes which are up and/or down regulated upon differentiation of neural crest cells into smooth muscle cells. The conditions suitable for smooth muscle cell differentiation include those as disclosed in particular with TGF-beta as noted in Figure 22 D-F and column 35, lines 47-63 and the cells are immortalized via v-myc transformation.

As to applicants new claim limitations, of expression of alpha-actin, calponin and SM22-alpha , it is noted that Anderson is silent to expression of alpha-actin and SM22-alpha . However as the transformed cells of Anderson are of a neural crest cell line immortalized via v-myc transformation, in the same manner as the preferred embodiment of the invention, and because Anderson's cells are differentiated into smooth muscle cells similarly to Applicant's, the cells would inherently and necessarily express alpha-actin, calponin and SM22-alpha. The specification and art recognize that alpha-actin, calponin and SM22-alpha genes are expressed in smooth muscle, see in particular p. 15, lines 23-28 of the specification. Similarly Anderson evidences that calponin and smooth muscle alpha-actin are expressed in smooth muscle cells. Both the cells of Applicants claims and Anderson are designated as smooth muscle cells. Therefore based on the specifications teachings that smooth muscle cells express alpha-actin, calponin and SM22-alpha and the teachings of Anderson that the cells are smooth muscle cells and express calponin and smooth muscle alpha-actin, the cells are established as being the same. As the cells are the same i.e., they are smooth muscle alpha-actin cells, both the cells of Applicant's invention and Anderson would necessarily and inherently express the noted smooth muscle genes alpha-actin, calponin and SM22-alpha, in addition to smooth muscle alpha-actin.

Thus absent evidence to the contrary, the teachings of Anderson that the cells of the '654 and '499 patents are smooth muscle cells would be sufficient for the artisan to

conclude that the cells would necessarily and inherently express the same genes established to be expressed in smooth muscle cells, namely alpha-actin, calponin and SM22-alpha as claimed, even though the reference only acknowledges expression of smooth muscle alpha-actin and calponin.

Moreover, it is noted that in TGF-beta cultures such as in Figure 22D-F, column, 5, lines 21-23 which teach 99% of the colonies (cells) in the TGF-beta cultures as being smooth muscle cells, see also column 36, lines 47-63. Such cultures are provided with and without TGF-beta. In at least the TGF-beta cultures, the smooth muscle cells are uniform as it is noted that 95-99%, i.e., nearly 100% of the cells are smooth muscle cells as claimed in claim 34. While the exemplary neural crest cells of Anderson are of rat origin, the specification makes clear that mammalian cells are embodied, see in particular column 5, lines 67-column 6, line 8, and thus Anderson is inclusive of murine neural crest cells as in claim 35. Thus, the reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al., US Patent 5,672,499, Anderson et al., US Patent 6,001,654, Rao et al., J. of Neurobiology 32:722-746, 1997 and Sommer et al., Neuron 15:1245-58, 1995.

Anderson et al., Patents '654 and '499 are as set forth above and teach the methods of claims 7, 32, 34 and 35. Including the suitability of the method of identifying up and down regulation of gene expression in neural crest cells using neural crest cell lines transformed with v-myc.

Anderson et al., does not teach the method of claim 7, wherein the cells are Monc-1 cells.

Rao et al., teaches immortalized neural crest stem cells via transformation with v-myc which cells are termed Monc-1 cells, see in particular Abstract.

Sommer et al., also teach immortalized neural crest stem cells via transformation with v-myc which cells are termed Monc-1 cells, see in particular p. 1249, column 1, lines 7-17.

Thus, one of skill in the art would have been motivated to substitute the Monc-1 cells of Rao and Sommer in the method of Anderson, based on Anderson's teachings of the suitability of such v-myc transformed neural crest cells in the study of up and down regulation of gene expression during differentiation to smooth muscle cells. The appropriate conditions of culture are disclosed in Anderson and Anderson exemplifies the success in the method as smooth muscle alpha-actin and calponin are disclosed as being up regulated while other neuronal or glial type genes are down regulated. Thus,

the cumulative reference teachings render the claimed invention obvious to one of skill in the art.

Applicants argue that the '499 and '654 patents fail to teach a method for identifying genes that are either up- or down-regulated during the differentiation of neural crest cells into smooth muscle cells. Applicants argue that neither Rao or Sommer replace such deficiencies.

Applicants arguments have been fully considered but are not persuasive. Applicants clarify that the method is one that identifies genes or the presence of genes that are up or down regulated in culture, i.e., that exhibit increased or decreased presence or expression. Such is clearly identified via the methodology disclosed in the Anderson patents. In particular, increased expression is detected via the presence or increase in antibody staining and the decreased expression is detected via decreased or an absence of antibody staining for the particular gene of issue. Thus, the reference teachings render the claimed invention obvious to the artisan.

11. Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al., US Patent 5,672,499, Anderson et al., US Patent 6,001,654, and Liang et al., US Patent 5,599,672.

Anderson '654 and '499 are as set forth above and teach the method of claim 7.

Anderson '654 and '499 fail to teach the method of claim 7 wherein the step of identifying genes includes differential display of mRNA from the neural crest and smooth muscle cell cultures and cloning of the genes that are up or down regulated as claimed in claims 8-9.

Liang et al., teach differential display and cloning of mRNA genes using two different cell populations or cell populations under differing conditions for the purpose of

identifying genes that are differentially expressed, i.e., that are differentially expressed via up and/or down regulation of gene expression within the cells. Liang teaches that such methodology is advantageous over other methods of analyzing gene expression due to the ability to perform the subtractive analysis in decreased time, with very small quantities of test samples and the ability to analyze multiple genes in a single tube analysis. These advantages are provided via the differential display procedure due to the use of polymerase chain reaction (PCR) analysis performed in a single tube. Liang also teaches the additional advantage of differential display in providing the ability to identify and clone new genes that are up or down regulated in the two populations of cells.

Given the teachings of Anderson '654 and '499 one of skill in the art would have been motivated to substitute the common practice of analyzing gene expression via antibody binding/detection analysis with the practice of analyzing gene expression via differential display due to the motivation in the art of the advantages of performing the analysis in less time with less test sample and the ability to analyze a greater number of genes as well as the ability to identify and clone new genes that are up or down regulated in the two populations of cells. One of skill in the art would have further expected success in such methodology given the relatively simple and widely used procedures of performing PCR analysis, cloning and differential display of the differentially expressed genes within the art. Thus, the reference teachings render the claimed invention obvious to the skilled artisan.

12. Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al., US Patent 5,672,499, Anderson et al., US Patent 6,001,654, Tagami et

al., Cell and tissue research, 245(2):261-266, 1986 and Kirschenlohr et al., Am. J. Physiol., 265, C571, 1993.

Anderson et al., '499 and '654 teach the addition of fetal bovine serum causes neural crest cells to differentiate into smooth muscle cells. The '499 and '654 patents additionally teach that 5% FBS or 1mg/ml FBS is sufficient quantity to produce such differentiation.

Anderson et al., '499 and '654 do not teach culture in 10% FBS.

Kirschenlohr et al., teach experiments conducted on human aortic vascular smooth muscle cells derived from healthy transplant donor tissue. The smooth muscle cells are cultured in standard optimal smooth muscle cell maintenance media comprising Dulbecco's modified Eagles medium (DMEM)+ either 10% fetal calf serum or 20% (FCS). The results exemplify that the proliferation of the smooth muscle cells is less with 10% FCS than 20% but that both are proficient for maintenace of smooth muscle cells in culture.

Tagami et al., teach that the artisan recognizes standard culture conditions for the amintenance of smoot-muscle cells in culture with the addition of 10-20% fetal calf serum to media to maintain viable cells.

Thus, given the cumulative reference teachings that 5% FCS is sufficient to produce smooth muscle cell differentiation but that 10%-20% FCS is optimal for maintenance of smooth muscle cells in culture, the skilled artisan would be motivated to maintain the differentiated smooth muscle cells in the maintenance media of Kirschenlohr at 10% FCS given the teachings that such is optimal for maintaining the cells in culture and the need to maintain the cells in culture for analysis via differential

display. One of skill in the art would have expected success given the well known maintenance conditions as disclosed in the art and the success in maintaining such cultures as evidenced via Kirschenlohr and Tagami. Thus, the reference teachings render the invention obvious to the skilled artisan.

Status of Claims

13. No claims are allowed.

Conclusion

14. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
June 27, 2002

Gary L. Kunz

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